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Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease (COPD)

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ABSTRACT

People with advanced COPD experience distressing physical and psychological symptoms, often have limited understanding of their condition, and infrequently discuss end of life issues in routine clinical care. These are strong indicators for expert multidisciplinary palliative care incorporating assessment and management of symptoms and concerns, patient and caregiver education, and sensitive communication to elicit preferences for care towards the end of life. The unpredictable course of COPD and difficulty predicting survival remain barriers to timely referral and receipt of palliative care. Early integration of palliative care with respiratory, primary care and rehabilitation services, with referral based on the complexity of symptoms and concerns, rather than prognosis, can improve patient and carer outcomes. Models of integrated working in COPD could include: services triggered by troublesome symptoms such as refractory breathlessness; short-term palliative care; and in settings with limited access to palliative care, consultation only in specific circumstances, or for the most complex patients.

Keywords: breathlessness, COPD, integrated care, palliative care, symptom management

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a major contributor to global morbidity and mortality.^{1,2} Despite declining rates in smoking in developed countries, tobacco consumption in low-to-middle incomes is increasing, and global COPD prevalence is projected to rise due to population growth and aging.³ The disease is characterised by chronic airflow limitation and symptoms of breathlessness, exercise intolerance and cough.⁴ The mainstay of pharmacological treatment is inhaled bronchodilator and anti-inflammatory therapies. These have modest effects on airflow limitation and rates of exacerbations, but not survival.⁵ COPD is recognised as a multi-system disease with impacts beyond the lung associated with symptom burden and prognosis.^{4,6,7} Further, many people with COPD have multiple other conditions. A recent meta-analysis of published literature found that COPD is associated with significantly higher comorbidities than other diseases.⁸ Thus, even when medical treatment is optimised, a significant proportion of people with COPD continue to experience symptom related distress.⁹ Hence, there is a clear role for additional intervention with the therapeutic aims to reduce symptoms, improve functioning and optimise quality of life.

Within this context, palliative care might be expected to play a prominent role in the management of people with COPD. Palliative care is “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering”.¹⁰ It puts the person before the disease, affirms life, and regards death as a normal process. Palliative care supports people to live fully through the early identification, and impeccable assessment and treatment of physical, psychosocial and spiritual concerns, providing education around illness to patients and families; and discussing treatment preferences towards the end of life (Figure 1).^{2,11} Evidence supporting involvement of palliative care in non-cancer conditions is growing, including early in the course of disease. A recent systematic review and meta-analysis pooling data on patients (n=12,731) and caregivers (n=2,479) demonstrated palliative care is associated with improvements in patient symptom burden (standardized mean difference SMD; -0.66; 95% CI, -1.25 to -0.07), quality of life (SMD 0.46; 95% CI, 0.08 to 0.83) over 1 to 3 months, and a consistent pattern of lower health care utilisation.¹²

Almost 20 years ago, the SUPPORT study of the seriously ill admitted to hospital, advocated for earlier and enhanced palliative care for people with COPD, including in those remaining open to life-sustaining treatments.¹³ However, there are barriers to palliative care referral in COPD and progress has been slow. The disease has an unpredictable course, punctuated by frequent exacerbations, and often without a distinct terminal phase.¹⁴ Clinicians are poor at predicting the survival of patients with COPD, even when they are hospitalised.^{15,16} Although composite prognostic indices such as the BODE and ADO can help,^{17,18} these lack the accuracy required to change short-term management of individuals (C statistics for survival 0.61 and 0.74), in part because they do not consider non-respiratory causes of death such as cardiovascular disease. It is therefore unsurprising that compared with other chronic illnesses people with COPD remain less likely to be referred to palliative care.¹⁹ Even in patients with advanced disease such as those on long term oxygen therapy or hospitalised with exacerbation, large cohort studies show only 2-20% have accessed palliative care services.^{19,20} Population based studies comparing symptom burden to palliative care receipt suggest this gap between COPD and other chronic illnesses is widening with time.^{21,22} leading to poorer quality end of life care.²³ People with COPD are more likely to die in a hospital setting compared with people with lung cancer,²⁴ which is against the general preference to die at home.²⁵ In a UK population-based study spanning 14 years, 67% of people with COPD died in hospital whilst 20% died at home, and <1% died in a hospice setting.²⁶

The aims of this review are to (i) describe the common physical and psychosocial symptoms and concerns of people with advanced COPD; (ii) summarise current evidence on how these can be addressed using palliative care interventions; and (iii) consider models of integrated palliative care in COPD and evidence for their effectiveness.

SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review were identified by searches of the Cochrane Library, MEDLINE and EMBASE databases. We used the search terms “palliative care”, “end of life”, “symptom”, “breathlessness”, “communication”, “advance care planning”, AND “respiratory” or “COPD”, and hand searched reference lists from retrieved articles. We considered articles published in English between 1980 and 2017, but predominantly selected publications from the past 5

years. When assessing the effectiveness of an intervention or service model, systematic reviews and meta-analysis were selected over individual randomised controlled trials, and where possible we extracted data or calculated effect sizes. When considering the symptoms, concerns and experiences of people with advanced COPD we selected observational and qualitative studies to support our interpretation of evidence.

COMMON EXPERIENCES OF ADVANCED COPD

The common experiences of people living with advanced COPD reveal multiple areas of need. A meta-synthesis of qualitative studies found that patients consistently report a limited understanding of their condition, a sustained symptom burden, and the unrelenting psychosocial impact of disease (Figure 2).²⁷ The slow onset of symptoms leads some patients to interpret COPD as a normal aging, and with its long course the seriousness of the disease is not always appreciated.²⁸ Patients may take a stoical approach to their symptoms, perceiving them as a “way of life” rather than components of progressive illness.²⁹

Patients with COPD report a median of 11-14 symptoms,^{30,31} which is a comparable number to patients with advanced lung cancer.^{32,33} Multimorbidity is common in COPD and symptoms may relate to, for example, concomitant heart failure or diabetes.³⁴ In a large cross-sectional study, almost half of patients with COPD aged over 65 had at least three other conditions.³⁵ This sustained symptom burden often results in patients focusing on maintaining or adapting to the present, rather than looking to the future.^{36,37}

The psychosocial impact of COPD is multifaceted and can be influenced by the disease, but also the shame and guilt that smokers who develop COPD can carry, sometimes reinforced by social attitudes.²⁷ Anxiety and depression are highly prevalent,^{38,39} and can exacerbate other symptoms including breathlessness. Conversely, breathlessness can limit patient function to such an extent that disability leads to isolation and loneliness. In open interviews patients describe the ‘invisibility’ of their problems.⁴⁰ It is easy for patients to feel demeaned by the limitations of the illness and question ‘why me?’. These feelings may lead people to feel unworthy of care, shun company, or not seek help.^{40,41} Younger patients with COPD, such as those with an inherited condition (alpha1-antitrypsin deficiency), may carry the additional burden of balancing illness with a young family and/or continuing employment. Up to 1 in 10 people with COPD report a loss of dignity; ‘the quality or state of

being worthy, honoured, or esteemed', which in cross-sectional studies is associated with requiring assistance to self-care, anxiety and depression, and being uncertain about future health care.⁴²⁻⁴⁴

ADDRESSING SYMPTOMS AND CONCERNS

For all symptoms, medical management of the underlying condition needs to be optimised and accurate diagnosis of contributing factors to symptoms must be elucidated. Optimal medical management of the stable patient with COPD comprises prevention strategies (smoking cessation, influenza / pneumococcal vaccination), reducing symptom burden and preventing exacerbations and hospitalisations. This has been summarised recently by the Global Initiative for Chronic Obstructive Lung Disease.⁴ In patients with advanced COPD, the mainstay of pharmacologic treatment is dual combination bronchodilator therapy, comprising long-acting beta 2 agonist and muscarinic antagonist (LABA/LAMA). These have modest benefits on FEV₁, health status, exercise tolerance and reduction of exacerbations, with additive benefits over monotherapy. Inhaled corticosteroids, used in conjunction with bronchodilator therapy, reduce exacerbations.⁴ To date however, no inhaled therapy has been shown to convincingly reduce long-term lung function decline or mortality.

Of the non-pharmacologic therapies, pulmonary rehabilitation, a multi-disciplinary program of care comprising exercise-training and education (particularly around self-management), significantly improves exercise tolerance, dyspnea, health status and psychological morbidity in those who are medically optimised.⁴⁵ Long term oxygen therapy is recommended in patients with COPD and severe hypoxemia,⁴⁶ but does not improve survival, exercise tolerance, symptoms or reduce hospitalizations in those with moderate hypoxemia or exercise-induced oxygen desaturation alone.⁴⁷ Ventilatory support is a standard of care for acute type II respiratory failure during severe exacerbations of COPD, but there is increasing evidence to support the use of domiciliary non-invasive ventilation in select patients with persistent hypercapnia following hospitalization.⁴⁸ Surgical options include lung volume reduction surgery which improves survival in select patients with heterogeneous upper-lobe emphysema and poor exercise capacity,⁴⁹ whilst lung transplantation in appropriate selected patients with very severe COPD has been shown to increase exercise capacity and quality of life.

Palliative care may be proposed to patients and families as an additional layer of expert support and can lead on or share symptom management with other teams.⁵⁰

Comprehensive symptom assessment using patient reported outcome measures helps to identify each individual's symptoms and concerns.^{51,52} This includes not only symptom severity but the impact on the patient's life and that of their carers. Symptom management can then be put in the context of the individual's situation with their own goals leading the direction of care. Management considerations for common symptoms in advanced COPD are provided in Table 1 with key references and supporting evidence. Treatable causes relating to disease management, e.g. cough due to ACE-inhibitors or dry mouth due to LAMAs, should be excluded and core practices, e.g. correct inhaler technique, should be reinforced. There is often a paucity of evidence specific to symptom control in COPD, so approaches may be based on cancer, though the trial evidence base for cancer-specific palliative care is only marginally greater. Standard texts provide more complete information.^{53,54} The cardinal symptoms of advanced COPD are breathlessness, fatigue and cough, which co-exist so frequently they are sometimes called the 'respiratory cluster'.⁵⁵

Breathlessness

Non-pharmacological interventions take priority in the mobile patient and can be helpful even in advanced disease.⁵⁶ Supporting patients to self-manage can increase their individual's self-efficacy and reduce feelings of helplessness in both patient and carer.⁵⁶ This can lead to a virtuous circle of reduced anxiety and depression, more activity and social contact, and improved quality of life. The following may have value for the mobile patient: increasing physical activity by means of activity pacing, mobility aids, and an individual exercise plan; use of the hand held fan or cold water spray to palliate the sensation of breathlessness;⁵⁷ breathing retraining;⁵⁸ and support for carers including education.^{59,60} Other interventions such as behavioural therapies or Tai Chi may be useful, depending on the individual and are worthy of further study.⁶¹ A written individualised 'crisis plan,' outlining actions to palliate breathlessness may enable the patient and carer to have a reminder of effective actions available when feeling overwhelmed by fear, or at moments of severe episodic breathlessness.⁶² These interventions have been combined into services for people with breathlessness that persists despite optimal management of disease (see Table 1 and 'Integration of palliative care and respiratory services').^{63,64}

The neurophysiology of breathlessness is complex and incompletely understood. The 'Breathing Thinking Functioning' approach can help to explain and choose component interventions.⁶⁰ In those with 'breathing' dysfunction, for example, specialist physiotherapy may be most appropriate. Breathlessness can be driven by unhelpful incorrect thoughts about breathlessness (patients might feel they are going to die during a breathlessness episode) or believe long-term resting will help reduce the symptom. The 'thinking' cycle may be dominant in that patient and to change these cognitions before doing anything else is likely most effective. Like many people living with a chronic relapsing and remitting disease, patients with COPD have higher levels of anxiety which in turn can exacerbate breathlessness. Anxiety and breathlessness are particularly linked because of the role the amygdala and higher cortical centres have in the genesis of both symptoms. Other patients may be most affected by the 'functioning' vicious circle; resting to avoid breathlessness, and so becoming deconditioned, breathless and fatigued at lower levels of function. Helping the patient to become more active will be the priority here, with pacing advice, goal setting and mobility aids as indicated.

There is limited evidence for most pharmacological approaches for breathlessness, and research is urgently needed into effective drug treatments (Table 1). Pharmacological treatments do not address the underlying cycles from psychosocial problems or unhelpful cognitions that may drive breathlessness, and therefore any pharmacological treatment may benefit from being combined with non-pharmacological treatments. The more severe and unremitting the breathlessness is, the more likely that pharmacological treatment is needed. Three main classes of drug are routinely used to palliate breathlessness: opioids, benzodiazepines and anti-depressants.

Opioids have the largest evidence base though it is not substantial. A recent Cochrane review and meta-analysis of the few small trials available concluded that 'There is some low quality evidence that shows benefit for the use of oral or parenteral opioids to palliate breathlessness, although the number of included participants was small.' There was no evidence to support nebulised opioids. Subgroup analysis including only those with COPD produced similar results. The review recommended that 'Further research with larger numbers of participants, using standardised protocols and with quality of life measures included, is needed'.⁶⁵ Ekstrom et al re-analysed these results as they believed that the

analysis 'did not account for matched data of crossover trials' (11/12 included trials), and on this basis argued that the true effect was larger than that found by the Cochrane review.⁶⁶ The Cochrane review of opioids for breathlessness did not report differences in survival or emergency room visits, but this was rarely studied. Some patients choose not to continue opioids because of adverse effects.⁶⁷ Some concerns have recently been raised regarding opioids for pain in COPD (see 'Pain' section). Taken together these findings suggest that in those patients where non-pharmacological approaches are no longer effective, opioids currently have the best evidence base among drugs to help refractory breathlessness especially in advanced disease, at the end of life and in the most severe breathlessness. They will not suit all and further research is needed especially in longer term effects. As with opioids used for pain relief, it is essential to seek and actively treat potential adverse effect such as nausea, vomiting and constipation.

Benzodiazepines, although widely used, have no evidence to support their use. They have a high potential for dependency and are very difficult to withdraw – with both physical and psychological dependence developing rapidly. A recent Cochrane review found no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer or COPD.⁶⁸ Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. In clinical practice therefore, benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. They may be suitable during anxiety and/or at the very end of life. There is a need for well-conducted and adequately powered studies.

Antidepressants have been mooted as possible treatments for breathlessness because of serotonergic pathways involved in the genesis of the symptom. Several trials have foundered because of the difficulties of drug interactions in patients with advanced disease who are taking a wide range of agents. Depression commonly accompanies breathlessness therefore there is a rationale for having a low threshold for using this group when there is accompanying depression. Many palliative care physicians favour mirtazapine (which is not a first line anti-depressant) because: (i) it is anxiolytic at low doses (ii) it is tetracyclic antidepressant that affects nor-adrenergic and serotonergic pathways in the brain stem –

both known to be involved in the central genesis of breathlessness. Fully powered trials are now needed.

There is no evidence to show that oxygen palliates the sensation of breathlessness in patients without hypoxia, though it may be essential for other disease-related morbidities such as hypoxia reducing exercise tolerance, or its association with cognitive impairment. A number of other drugs have been tried (e.g. cannabinoids, furosemide, heliox) in the management of breathlessness, but none can be recommended outside a clinical trial.

Fatigue

Fatigue is a profound feeling of physical and psychological weariness not relieved by sleep or rest. Fatigue management has some overlap with breathlessness. Both require psychological approaches and, paradoxically for patients, increased physical activity can be helpful. Sleep quantity and quality is important, and often reported to be poor. A complete assessment is essential, paying attention to physical activity, psychological status, beliefs and sleep habits⁶⁹. Providing education to support self-management,⁷⁰ improving the patient's psychological resilience, and addressing depression are key to improving fatigue.⁷¹ Individualised exercise and rehabilitation plans may improve physical activity and independence in daily activities⁷². Based on limited evidence, no drug treatment can currently be recommended, though research is focused on modafinil and methylphenidate.⁷³

Cough

Cough can be very distressing for patients. Optimal respiratory management includes mucolytics treating infection, and sputum clearance physiotherapy as appropriate.⁷⁴ Non-pharmacological treatments for refractory cough may include patient education on cough reflex hyper-sensitivity and the effect of repeated coughing, laryngeal hygiene and hydration, e.g. through use of nasal breathing, cough control techniques, and psychoeducation counselling.⁷⁵ Birring et al. combined these in a complex Physiotherapy and Speech and Language Intervention (PSALTI), which in a randomised controlled trial (n=75) reduced cough frequency and improved patient quality of life.⁷⁶ Although delivered using therapist expertise, written treatment guidelines and prompt sheets may improve

availability and support use by other clinicians.⁷⁵ Based on limited evidence, no antitussive drug treatment can currently be recommended. Evaluation of centrally acting neuromodulator drugs such as Gabapentin, widely used for refractory cough, is needed for COPD.⁷⁷ There are promising antitussives in development for refractory cough such as P2X3 antagonists that target cough sensory nerves; which should be evaluated for use in COPD.⁷⁸

Pain

Pain can be related to the systemic impacts of COPD and its management (e.g. osteoporosis due to long-term steroid use), and pre-existing co-morbidities (such as osteoarthritis).⁷⁹ Long-term pharmacological management of chronic non-malignant pain is challenging and needs to be individualised. Assessment of the cause and relieving factors of pain is key, and many patients may have several different pains, each with a different aetiology. Cicely Saunders, founder of the modern hospice movement, developed the concept of ‘total pain’ with physical, emotional, spiritual and social components, all of which must be considered in any assessment.⁸⁰

Pain management in chronic illness has advanced considerably in recent decades. The WHO approach of an “analgesic ladder” with non-opioid analgesics (step 1), followed by a mild opioid (step 2) and strong opioids (step 3) in patients with persistent pain remains at the cornerstones of practice.⁵⁰ Non-opioid drugs (including non-steroidal anti-inflammatory drugs –NSAIDs) are effective analgesics for patients with mild pain and can be combined with opioids in patients with moderate to severe pain. Drugs should be given orally (wherever possible) and regularly, rather than waiting for pain to break through. Opioid treatment should be at the lowest effective dose.⁸¹ It should slowly titrate to individual patient need, calculating the previous 24 hour dose by summing the regular plus ‘as required’ doses. There are newer analgesics, different routes of administration (e.g. sublingual, subcutaneous, transdermal, intra-nasal), long and short acting medications for different pain durations, techniques to manage neuropathic pain and research into approaches to “switch” opioids, which may be useful if side effects are problematic, in instances of renal failure and, in some cases, to improve effectiveness of pain relief or in cases when the person responds poorly to morphine because of their genetic makeup. However, most of this research is among patients with cancer or musculoskeletal pain, and

evidence in COPD is limited.⁸² Common side effects should be managed and explained, including constipation, drowsiness and nausea/vomiting.

A retrospective cohort study using routine data from Canada recently raised some safety concerns regarding opioid use for pain relief in COPD, although the analysis focussed on people not in advanced stages of disease. The authors used propensity scoring to try to reduce the effects of sample biases (e.g. people prescribed opioids for pain being different from those not being needed this treatment). Patients prescribed opioids had higher emergency room visits and mortality compared to those who did not (Hazard Ratios (HR) all-cause mortality 1.76, 95% CI 1.57–1.98), but had lower outpatient exacerbations (HR 0.88, 95% CI 0.83–0.94).⁸³ A longitudinal, population-based study of patients starting long-term oxygen therapy from Sweden also studied opioid prescribing in COPD, and found that most prescriptions (97%) were for pain, with only 2% for breathlessness, 1% other.⁸⁴ Patients and clinicians commonly express concerns about dependence and addiction from opioids,⁸⁵ yet the event rate for addiction and abuse is very low.⁸²

PSYCHOLOGICAL AND SOCIAL CARE

The distress of living with COPD is widely recognised but can be difficult to address in clinical practice, with calls for ‘more holistic care’ from those involved in clinical standard setting.^{4,86} Going beyond physical symptoms and treating the whole person is important, as patients living with advanced disease place high value on achieving a sense of control, strengthening relationships with loved ones, maintaining dignity, and coming to peace spiritually.^{44,87,88}

An important role of the clinical team includes countering any self-blaming cognitions that can heighten the chances of rumination and depression. Psychological and/or lifestyle interventions, including exercise, can be used to help improve anxiety and depression in COPD.^{89,90} Cognitive behavioural techniques are increasingly incorporated within pulmonary rehabilitation programmes, psychologists are often part of the respiratory team, and specialist nurses or physiotherapists are now more likely to use psychological strategies as part of care than was previously seen.⁹¹ There is still uncertainty about when pharmacological intervention is needed or which strategies are most effective.⁹² Dignity conserving therapy and spiritual support (in its broadest sense) can also reduce the loss of self-esteem and feeling a burden to others. Dignity therapy also provides an opportunity for

people to reflect on things that matter. It uses questions like ‘what would you want your family to know and remember about you?’, ‘what are your most important accomplishments/at what times did you feel most alive?’ and ‘what have you learned that you would want to pass on to others?’⁹³ Trials of dignity therapy as conducted in cancer are required in COPD.^{93 94}

As well as managing psychosocial morbidity, we suggest that improving resilience and well-being in people living with COPD is also important. Emerging evidence suggests that enhancing psychological well-being may attenuate the inflammatory response.⁹⁵ The ‘five ways to well-being’ provides one framework to support patients and their families, and emphasises the importance continuing to exercise (*be active*), being open to a non-judgemental, more compassionate awareness of current reality (*take notice*), learning new skills (*keep learning*), and remaining connected to a wider social network (*connect*). The reminder to remain altruistic (*give*) reinforces that patient’s feel psychologically enriched by being engaged with the needs of others. Benzo et al’s work suggests higher levels of Emotional Intelligence are also associated with better outcomes regardless of age or disease severity.⁹⁶

Support for carers, family members and those close to the patient

The disability, uncertainty and emotional toll associated with COPD can inflict a heavy burden on caregivers, families and those close to the patient, who may have health problems of their own, resulting in persistent stress and physical demands. The psychological care and support of the family and caregivers has recently been reviewed in depth.^{97,98} One of the problems supporting carers is that they are rarely identified, although patients living with a carer are shown to have fewer exacerbations and admissions.^{97,99} The first step is therefore to identify carers (who may not be cohabitants) and their roles.⁹⁸ Carer support can include: assessment and active treatment of depression and anxiety; education around the disease, symptoms, and relationship management; and bereavement support.¹⁰⁰ It can be valuable to acknowledge the positive aspects of caregiving, such as personal growth and a deepened relationship.¹⁰¹

COMMUNICATION AND CARE PLANNING

Need for improved communication

In qualitative studies patients with COPD commonly express concern about the lack of education around disease progression and end of life, which can prompt anxiety around what the end of life will entail.^{27,102} End of life issues are infrequently discussed.¹⁰² In representative observational studies only 1 in 6 patients with advanced COPD,¹⁰³ and 1 in 3 patients dependent on oxygen,¹⁰⁴ had discussed life-sustaining treatments, prognosis, the dying process, or spirituality. When end of life discussions do occur, the quality of communication is rated highly, suggesting the key to improving communication is to overcome initial barriers to these discussions taking place.¹⁰² From systematic reviews, patient-reported barriers include a lack of understanding about their condition, and a belief that health care professionals will initiate discussions about end of life care at the appropriate time.^{104,105} Health care professional barriers include a lack of time and communication skills, uncertainty around prognosis, feeling that end of life discussions conflict with disease management, and not wanting to dispel hope.^{104,105} Fragmented care between acute and primary care services can also result in a diffusion of responsibility where no one is sure who should initiate conversations about end of life care.¹⁰⁵

Talking about End of Life Care and meeting preferences

Narrative reviews suggest that discussion and education about the course of disease, prognosis, care preferences, and spiritual issues are valued by people with advanced COPD.^{106,107} Care preferences towards the end of life may concern which life-sustaining treatments patients wish to receive or not (e.g. tube feeding, mechanical ventilation and cardio-pulmonary resuscitation),¹⁰³ where they would prefer to receive care, and the location in which they may choose to die.¹⁰⁷ End of life discussions are not associated with increased distress, worry or depression,¹⁰⁸ but are associated with care being more consistent with patient preferences, less aggressive care at the end of life, earlier hospice referral, and improved family bereavement.¹⁰⁹ Discussion is recommended early on to ensure subsequent care is in keeping with the patient's preferences should they lose capacity to express them.¹⁰⁹

Best practice for end of life communication comprises exploring illness understanding, eliciting decision-making preferences, understanding patients' priorities and goals, exploring

views on trade-offs and wishes for family caregiver involvement, and sharing information about prognosis (including uncertainty) in line with their preferences.^{109,110} Awareness of individual communication preferences is crucial, as whilst most patients express openness to end of life issues, this is not always the case. Health professionals should be sensitive to the preference not discuss end of life care, and provide ongoing opportunities to revisit it.¹¹¹ When discussing end of life, some patients want explicit information while others prefer the 'bigger picture' and are ambivalent about likely prognosis.^{112,113}

The dynamic or unstable nature of preferences should not be underestimated. In stable outpatients with advanced COPD, about one-third of patients change their preference for life-sustaining treatments over one year, and two-thirds change their willingness to accept these treatments.^{101,114} There can be a tension between wishing to die at home (which most people prefer) and being admitted to hospital, especially when the chance of survival following hospital treatment is high – the SUPPORT study found that inpatient mortality in people with COPD admitted in respiratory failure was 11%.¹³ This makes the decision not to admit (or not be admitted) very difficult, especially as it is not possible to predict survival even in the acute situations.^{15,16} It is not known to what extent people with COPD change their preferences for place and goals of care, once they are in the midst of an exacerbation.

Discussions about end of life care may occur as part of an Advance Care Planning (ACP) process. ACP interventions aim to improve and often document communication between the patient, their family, and healthcare professionals about their values and preferences for end of life care.¹¹⁵ In patient populations, a systematic review of 55 randomised controlled trial found that ACP led to increased discussion of end of life issues between patients and their health care professionals (OR 2.82 [95% CI 2.09-3.79]) and increased completion of advanced directives (OR 3.26 [95% CI 2.00-5.32]).¹¹⁶ Only three studies reported the effect of ACP on subsequent care and all found it closed the gap between patient preferences and subsequent care delivery. Two further studies, including one using an ACP-related patient feedback form with people with COPD,¹¹⁷ found ACP quality of communication.¹¹⁶ Given the diversity and complexity of ACP interventions it is important to remain cautious about implementing specific interventions. With few studies examined the effect of ACP on subsequent care and only one study focused on patients with COPD, future research on effectiveness on patient and family outcomes is needed.

INTEGRATING PALLIATIVE CARE IN COPD SERVICES

Indications for palliative care

Guidelines suggest that palliative care should begin at the time of diagnosis of a life-limiting illness, recognising that symptom control is key to ensuring optimal quality of life.^{4,50} The American Thoracic Society endorses the concept that palliative care should be available at all stages of illness, and emphasises the value of palliative care including when curative or restorative treatments are being offered.⁵⁰ In the US, patients with COPD are eligible for hospice benefit under Medicare if they meet criteria for the terminal stage of pulmonary disease (life expectancy 6 months or less) of; severe chronic lung disease with disabling breathlessness at rest and decreased functional capacity, plus progression as evidenced by visits to the emergency department or hospital admission.⁵⁰ Most insurers require the physicians to certify that they expect the patient to die within 6 months. The uncertainty around prognostication seemingly leads to referral delay, with almost one-third of patients dying within one week of referral.⁹

We advocate for early integration of palliative care with respiratory, primary care and rehabilitation services, and referral based on complexity of symptoms and concerns, rather than estimated prognosis. Early integration allows longer for established relationships between palliative care staff and patient, and avoids crisis management during impending death.¹¹⁸ Expertise from the palliative care team, with the required skills for managing complex psychological, social, and emotional aspects of illness, may also release time for the respiratory physician to focus on medical management.¹¹⁹ Alongside symptom severity,^{63,64} indicators of deterioration that can be used to trigger referral, include hospitalisation with an exacerbation (particularly with respiratory failure requiring mechanical or non-invasive ventilation), declining functional status, and co-morbidities.^{120,121} Qualitative studies find these criteria are acceptable to patients and their families.^{62,122}

Integration of palliative care in COPD services

Models that integrate palliative care with existing services are needed, such as those being implemented in oncology.¹²³⁻¹²⁵ In most countries, palliative care teams in hospital and community settings provide the majority of patient contacts. Teams in hospice settings may

offer respiratory clinics, rehabilitation services, and provide care for people with COPD at the end of life, though the proportion of patients seen in the hospice setting remains small.²⁶

Randomised controlled trials provide good quality evidence that early integration of palliative care with respiratory and/or primary care services can alleviate the effects of breathlessness on quality of life and its distress, in patients with COPD and their families, without increasing overall costs of health, social and informal care.^{63,64} In one trial there was also improved survival, as a secondary outcome, and improved dignity and patient and family satisfaction.¹²² Service specifications of these case-examples are detailed in Table 2, which often involve short-term early integration of palliative care. In a small feasibility trial, patients were randomised to usual care or a nurse-led palliative care intervention 4 weeks following hospital discharge.¹²⁶ In this context the additional intervention overlapped considerably with respiratory discharge planning,¹²⁷ and few new actions were instigated.¹²⁶

Other interventions have been implemented as quality improvement programmes but not tested in controlled settings. Rocker and Cook's "Implementing a Novel and Supportive Program of Individualised Care for Patients and Families Living with Respiratory Disease" (INSPIRED) model of care includes an action plan, advance care planning, and use of low dose opioids in advanced COPD. The program aims to support people to die at home, and initial service evaluations suggests a reduction in unplanned hospital admissions can be achieved.^{128,129} Advanced COPD clinics led by respiratory medicine with palliative care consultation only for the most complex patients have also been described,¹³⁰ but again require formal testing. Figure 2 summarises models of integrated palliative care, based on examples identified in our literature search.

Integration of palliative care with pulmonary rehabilitation

A pulmonary rehabilitation (PR) programme typically comprises >25 hours of face-to-face contact with a health care professional representing an opportunity to provide treatments to address symptoms and concerns, educate around disease- and self-management skills, and to introduce palliative care if indicated. Some goals of PR and palliative care overlap. Both services target symptom management, functional independence and quality of life. Both address psychological concerns, especially around breathlessness using non-

pharmacological and education interventions. Heffner et al. surveyed patients (n=105) entering PR about the addition of advance care planning within the programme education, and found nearly 90% desired more information about advance directives and nearly 70% wished to discuss life-sustaining treatments more explicitly with their clinical team.¹³¹ The broader integration of palliative care into PR, could be one approach to introduce palliative care early on in illness,¹³² and warrants further study.

However, PR's reach is limited by poor uptake, variable service availability and non-completion, typically due to illness and co-morbidities. Epidemiological studies suggest that only a proportion of eligible patients receive and/or complete pulmonary rehabilitation; less than 50% of those referred in a recent snapshot audit of PR services in England and Wales.¹³³ Physically frail patients are less likely to complete PR.¹³⁴ The breathlessness services described above, and/or less intensive exercise modalities e.g. neuromuscular electrical stimulation^{135,136} may serve as alternative interventions for those unable to complete PR, or when effects of PR wane.¹³⁷ Further research is warranted to explore how palliative care might integrate with PR.

CONCLUSIONS AND POLICY IMPLICATIONS

People with advanced COPD experience complex often severe physical and psychological symptoms, fluctuating trajectories, significant illness burden for them and their families and multimorbidity. Palliative care is an approach that focuses on the whole person, with impeccable assessment and management of symptoms and concerns, supporting the person and those close to them. Modern approaches to palliative care, which are need rather than prognosis based, are especially suited to care for people with COPD, where prognostication is uncertain. There is emerging evidence for non-pharmacological and pharmacological treatments to aid the management of symptoms such as refractory breathlessness, depression, fatigue. Alongside and often after known effective treatments such as pulmonary rehabilitation, palliative care services can be integrated early in the course of illness using short-term models, and these can improve patient outcomes. However, unfortunately, few people with advanced stages of COPD receive any form of palliative care.

The findings of our review suggest that both health care professionals and policy makers should pay particular attention to improving access to palliative care for patients with COPD

and their families. This includes better training and support in the detection and management of symptoms and in communication skills. Such an approach may also focus on gaining a better understanding of preferences, and investing in services to enable more people to die in their preferred place of death, and ensure quality palliative care is available in locations (such as hospitals) where large proportions of this population die. Integrating palliative care earlier in the disease trajectory may be one route to achieve this. Investment into demonstration projects at the population level should be boosted.

Finally though, our review also identifies multiple gaps in the evidence, especially in therapies to alleviate symptoms such as breathlessness, and to support patients and families. There is a lack of evidence about the cost-effectiveness and safety of non-pharmacological and pharmacological therapies, which needs to be addressed through randomised trials and population-based cohort studies. Investment in research to discover and test better ways to manage the problems encountered in advanced COPD, such as symptoms, meeting preferences and supporting patients and families is urgent.

TABLE 1. Management considerations for symptoms and concerns in COPD

Symptom (prevalence estimate)	Management considerations	Supporting evidence
Breathlessness (32-98%) 33,138	Pulmonary rehabilitation	Stable disease: CRQ dyspnoea, MD 0.79 (95% CI 0.56 to 1.03), (19 trials, n=1283); CRQ mastery, MD 0.71 (95% CI 0.47 to 0.95), (19 trials, n=1212) ⁴⁵ Following hospitalisation: CRQ dyspnoea, MD 0.97 (95% CI 0.35 to 1.58), (5 trials, n=259); CRQ mastery, MD 0.93 (95% CI -0.13 to 1.99), (5 trials, n=259) ¹³⁹
	Multi-professional integrated breathlessness services	CRQ mastery, MD 0.58 (0.01 to 1.15), (1 trial, n=105) ⁶³ NRS distress due to breathlessness, MD -0.24 (95 % CI -1.30, 0.82), (1 trial, n=87) ⁶⁴
	Component interventions including breathing techniques, hand held fan, activity pacing, mobility aids, and support/ education for family and caregivers (including crisis plan)	Breathing techniques: 6 minute walk distance, MD 45 metres (95% CI 29 to 61) (2 trials, 74 participants) ⁵⁸ Hand-held fan: VAS breathlessness severity, MD -7.0 mm (95% CI -2.5--11.7), (1 trial, n=50) ⁵⁷ ; Borg score breathlessness, MD -0.08 mm (1 trial, n=70) ³¹ Activity Pacing and support/ education for family and caregivers: Expert opinion ⁶²
	Cognitive Behavioural Therapy, Tai Chi, Yoga	Cognitive Behavioural Therapy: CRQ dyspnoea, MD 4.4, (1 trial, n=222); CRQ mastery, MD 2.6, (1 trial, n=222) ¹⁴⁰ Tai Chi: CRQ dyspnoea, MD 0.05 (95% CI -1.32 to 1.42); CRQ mastery, MD -0.89 (0.30 to 1.47), (2 trials, n=48) ⁶¹ Yoga: CRQ dyspnoea, MD 1.60 units (95% CI -3.10 to 6.30 units), (1 trial, n=29) ¹⁴¹
	Low-dose oral or parenteral opioids	Change in dyspnoea score, SMD -0.09 (95% CI -0.36 to 1.19), (7 trials, n=214) ⁶⁵ Post treatment dyspnoea score, SMD -0.28 (95% CI -0.5 to -0.05) (11 trials, n=318) ⁶⁵ Reanalysis of above accounting for crossover: SMD -0.32 (95% CI -0.47 to -0.18), (17 trials, n=283) ⁶⁶
	Benzodiazepines	Breathlessness at rest, SMD -0.10 (95% CI -0.42 to -0.21), (5 trials, n=156) ⁶⁸

		Breathlessness at rest versus morphine, SMD -0.68 (95% CI -2.21 to -0.84), (2 trials, n=107) ⁶⁸ No evidence for or against benzodiazepines but can cause drowsiness
	Oxygen	NRS change morning, 0.9 points (95% CI -1.3 to -0.5), (1 trial, n=239) ¹⁴² NRS change evening, -0.3 points (95% CI -0.7 to 0.1), (1 trial, n=239) ¹⁴² No consistent differences between groups in the change from baseline in measures of quality of life, anxiety, depression, or in distance walked in 6 minutes. (1 trial, n=738) ⁴⁷
Fatigue (23-96%) 33,143,144	Pulmonary rehabilitation	Stable disease: CRQ fatigue, MD 0.68 (95% CI 0.45 to 0.92), (19 trials, n=1291) ⁴⁵ Following hospitalisation: CRQ fatigue, MD 0.81 (95% CI 0.16 to 1.45), (5 trials, n=259) ¹³⁹
	Self-management education programmes	CRQ fatigue, MD 2.0, (1 trial, n=135) ¹⁴⁵
	Activity pacing and good sleep hygiene	Expert Opinion
	Oxygen	No consistent differences between groups in the change from baseline in measures of quality of life, anxiety, depression, or in distance walked in 6 minutes. (1 trial, n=738). ⁴⁷
Anorexia (64-67%) 33	Nutritional supplementation (for patients with evidence of malnutrition)	Body weight change, MD 1.65 kg (95% CI 0.14 to 3.16), (11 trials, n=325). ¹⁴⁶
	Megestrol acetate	Body weight change, MD 2.5kg, (1 trial, n=145). ¹⁴⁷
Pain (21-77%) 33,148	Principles of WHO analgesic ladder	Expert Opinion
Depression	Complex interventions, cognitive behavioural therapy or multi-component	Complex interventions: Symptoms of depression, SMD -0.28 (95% CI -0.41 to -0.14),

(7-77%) 33,38,149	exercise training	(29 trials, n=2063) ⁸⁹ Cognitive Behavioural Therapy: Symptoms of depression, SMD -0.00 (95% CI -0.17 to 0.16), (7 trials, n=513) ⁸⁹ Multi-component exercise training: Symptoms of depression, SMD -0.47 (95% CI -0.66 to -0.28), (14 trials, n=1009) ⁸⁹
	Antidepressant medications	Treatment of case depression, OR 2.33 (95% CI 1.80-3.00), (25 trials, n=1674). ¹⁵⁰ Selective serotonin reuptake inhibitors (SSRIs) best tolerated
	Psychological interventions including CBT	Symptoms of depression, SMD -0.37 (-0.86 to 0.11), (4 studies, n=193) ¹⁵¹
Anxiety (10-55%) 33,39,149	Psychological therapies	Beck Anxiety Inventory change, MD -4.41 (95% CI -8.28 to -0.53), (3 trials, n=319) ¹⁵²
	Pharmacological interventions	"It is not possible to draw any conclusions for treatment. This review highlights the paucity of data in this area" (4 trials, n=40) ¹⁵³
Cough (45-70%) 154	Complex Physiotherapy and Speech and Language Intervention (PSALTI)	Cough Frequency per hour (fold change), MD 0.59 (95% CI 0.36 to 0.95), (1 trial, n=75); LCQ, MD 1.53 (95% CI 0.21 to 2.85), (1 trial, n=75) ⁷⁶
	Pregabalin or gabapentin	Pregabalin and speech pathology treatment: LCQ, MD 3.5 (95% CI 1.1 TO 5.8), (1 trial, n=40) ¹⁵⁵ Gabapentin: LCQ, MD 1.80 (95% CI 0.56 to 3.04), (1 trial, n=62) ¹⁵⁶
Daytime sleepiness and insomnia (15-77%) 33,157,158	NIPPV for hypercapnic patients with stable disease	Sleep efficacy (time asleep as percentage), MD -9.11 (95% CI -38.09 to 19.86), (3 trials, n=24) ¹⁵⁹
	Establish good sleep hygiene	Expert Opinion. ¹⁶⁰

	Cognitive behavioural therapy	Sleep latency, MD 19.03 minutes (95% CI 14.12 to 23.93), (20 trials, n=1162); Total sleep time, MD 7.61 minutes (95% CI -0.51 to 15.74), (20 trials, n=1162). ¹⁶¹
	Benzodiazepines	Sleep latency, MD -11.35 minutes (95% CI -18.24 to -4.46), (4 studies, n=130); Total sleep time, MD 0.84 minutes (95% CI 0.54 to 1.14), (6 studies, n=180) ¹⁶² May improve sleep duration but with adverse effects short term use recommended.
Dry mouth (71%) 163	Topical therapies: oxygenated glycerol triester spray	VAS for mouth dryness, SMD 0.77 (95% CI 0.38 to 1.15), (2 trials, n=115) ¹⁶⁴
Sexual dysfunction (79%) 165	Exercise therapy and education, advice on positioning	Expert opinion ¹⁶⁶
	Pharmacological management	Sexual function (International Index of Erectile Function), MD 6.8 (95% CI 0.57 to 13.03), (1 trial, n=29) ¹⁶⁷ Sexual satisfaction (7 point Likert scale), MD -0.3 (-1.42 to 0.82), (1 trial, n=29) ¹⁶⁷

Legend. Comparisons are versus usual care or no treatment control unless stated otherwise. CRQ = Chronic Respiratory Questionnaire; LCQ = Leicester Cough Questionnaire; MD = mean difference; OR = odds ratio; SMD = standardised mean difference; VAS = Visual Analogue Scale; WHO = World Health Organisation

Table 2: Structure and components of Integrated Palliative care and Respiratory services for patients affected by breathlessness

	King's College Hospital Breathlessness Support Service	Cambridge Breathlessness Intervention Service
Staffing	<ul style="list-style-type: none"> • Clinical Specialist Physiotherapist • Clinical Specialist Occupational Therapist • Palliative Care Nurse • Palliative Care Social Worker • Respiratory Medicine Consultant • Palliative Medical Consultant 	<ul style="list-style-type: none"> • Clinical Specialist Occupational Therapist (clinical co-ordinator/joint clinical lead with consultant) • Clinical Specialist Physiotherapists (one of whom also works as part of respiratory medicine department 2 days per week) • Palliative Medical Consultant • Access to Specialist Psychologist
Patients seen	Patients with advanced disease that is refractory to optimal medical management, and breathlessness on exertion or at rest	Patients with any diagnosed cause of breathlessness, who could benefit from a self-management programme, with any diseases
Referrals	From respiratory medicine, cardiac medicine, physiotherapy, palliative care or primary care via electronic record system, or letter	From any clinician in hospital or community via electronic record system, letter, phoned referral if urgent
First appointment	Typically 2-4 weeks	Typically 3-4 weeks, telephone advice may be given before
Face to face contacts	2 clinic visits, 1 home visit	2-4 home visits
Phone contacts (patient plus other care providers)	3-4	3-4
Average length of service contact	4 weeks	4-8 weeks
Service outcomes	Mastery of breathlessness assessed by Chronic Respiratory Questionnaire, breathlessness severity by Borg and Visual Analogue Scale, Palliative care needs and symptoms by Palliative Care outcome Scale (POS), London Chest Activity of Daily Living Scale, functional exercise performance by 6 minute walk test, and carer burden by Zarit Burden Inventory	Anxiety, breathlessness, satisfaction with service assessed by Numerical Rating Scales, self-report of improvement in specific areas nominated by patient
First stage or contact interventions	Respiratory medicine physician: <ul style="list-style-type: none"> • explore the symptom of breathlessness and its triggers • establish underlying cause of breathlessness • optimise disease-orientated management (check medications used correctly, appropriate treatments) • review of previous investigations • verbal and hand-written handover of notes from respiratory to palliative medicine physician to ensure patients do not have to repeat information 	Multidisciplinary team meeting to decide most appropriate clinician to see patient and/or carer: <ul style="list-style-type: none"> • Breathing Thinking Functioning (BTF) drivers to breathlessness prioritised after comprehensive assessment and used to set goals • Initial medical assessment more common with patients with cancer or complex medical problems <p>Addition intervention prioritised in line with BTF assessment or as marked</p>

	<p>Palliative medicine physician:</p> <ul style="list-style-type: none"> • experience of breathlessness • development of crises plan • burden on patient and family • symptom burden (other than breathlessness), with recommendations to patients and GP of any appropriate treatments • psychosocial & spiritual issues • introduction of non-pharmacological measures such as the hand-held fan, water spray <p>Breathlessness pack, with information leaflets on managing breathlessness, a 'poem' and chart of positions to ease breathlessness (laminated, to put up in the house and to read and follow when in acute breathlessness), fan/water spray</p>	<ul style="list-style-type: none"> • explanation and reassurance (always) • psychological support (always) • hand-held fan (always) • information fact sheets (subject prioritised by BTF assessment) • anxiety management • emergency plan • positioning to reduce work of breathing (rest, recovery and activity) • breathing control • education to patient and carer • pacing and lifestyle adjustment • assessment for and provision of mobility aids • individualised exercise plan, e.g. walking with pedometer • relaxation and visualisation • airway clearance techniques • advice regarding nutrition and hydration • support to family and patient to utilise education and self-management programmes • resources to help build social contacts • advice to carer about importance of looking after their own health • sleep hygiene (always assessed) • smoking cessation prompt • brief cognitive therapy • pharmacological review • well-being intervention • hypnosis • mindfulness CD • other resilience building e.g. five ways to wellbeing framework
Follow-up interventions (based on the patient's need as assessed and /or following review of first stage interventions)	<p>Physiotherapist:</p> <ul style="list-style-type: none"> • review of positions to ease breathlessness • provision of a walking aid • breathing control techniques and anxiety-panic cycle • education on management of exacerbations • home programme of exercise (DVD, personalised sheet) • cough minimisation techniques 	<p>Palliative medicine consultant:</p> <ul style="list-style-type: none"> • further pharmacological review e.g. low dose opioids, anti-depressants, anxiolytics <p>All team members</p> <ul style="list-style-type: none"> • monitoring of extent to which goals set at first meeting attained • implementation of new strategies depending on need.

	<ul style="list-style-type: none"> • pacing and fatigue management • sputum clearance techniques • ambulatory oxygen assessments <p>Occupational therapist:</p> <ul style="list-style-type: none"> • assessment of activities of daily living, mobility and transfers • assessment for aids and minor adaptations and referral for provision of equipment • wheelchair prescription • education on planning, pacing and energy conservation techniques to patients and carers <p>Social worker:</p> <ul style="list-style-type: none"> • carer assessment including understanding of disease and symptoms, information needs and coping strategies <p>Palliative medicine physician:</p> <ul style="list-style-type: none"> • re-evaluation of breathlessness and other symptoms • check use of fan, spray, pack, DVD, further guidance given • change of medications recommended if required, with contact with GP regarding future planned treatments if required • provided with information on drop-in patient/family information centre for further resources 	
Documentation	<ul style="list-style-type: none"> • Individualised letter addressed to patient (to reinforce self-management) summarising progress made, further recommendations and plan • Copy sent to the referring clinicians and the general practitioner • Summary to patient of any outpatient consultation with medical consultant • discharge summary to referrer with copies to GP, specialist services the patient was already in contact with (e.g. respiratory physicians), other involved health care professionals (e.g. district nurses, nursing home care staff) 	
Onward referrals	<ul style="list-style-type: none"> • Pulmonary, cardiac, community or hospice rehabilitation services • Specialist dietetic or psychological services • Hospice day or breathlessness services • Third sector support services e.g. Maggie's Centres, Breathe Easy 	

Contributors

MM and **IJH** are the overall guarantors of this manuscript and take responsibility for the content, including the data and interpretation. All authors contributed to a first draft of the manuscript, took the lead in writing specific sections, critically revised the manuscript, and approved the submitted version.

Declaration of interests

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